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Clinical Outcomes of Estrogen Negative-Progesterone Positive Invasive Breast Cancer, Retrospective Study

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Abstract: ***Background: Breast cancer is comprised of a heterogeneous subtypes. The decisions of treatment depend on the tumor expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER 2). These biomarkers have prognostic and predictive significances. Material and methods: 100 patients from 2008 to 2012 were identified and analyzed. Patients were classified into three hormonal receptors subtypes: ER-/PR+, ER+/PR±, and ER-/PR-. Analysis of the clinicopathological features, treatment, recurrence, survival rate and prognostic factor were compared. Results: The subtype ER-/PR+ was seen frequently in young age with large size tumor and lymph node metastasis, higher stage and histologic grade when compared with the other two subtypes. Analysis of the frequency of recurrence revealed that local recurrence, distant metastasis and number of deaths did not differ statistically and hence no difference in disease free survival (DFS) and overall survival (OS). The 5 years DFS was 37.5% , 20.3% and 21.7% in ER-/PR+ , ER+/PR± and ER-/PR- groups respectively. Conclusion & Recommendation: The breast cancer subtypes according to the ER and PR are biologically and clinically different groups. Assessment of PR is recommended as it can provide important prognostic information and prediction of response to adjuvant HT in ER- tumors.***

Keywords: breast cancer, hormonal subtypes, survival outcome

1. Introduction

Breast cancer is one of the tumors that have a number of heterogeneous subtypes with different clinical behavior and outcomes. Treatment decisions are based on tumor expression of the ER, PR, and HER 2. These biomarkers have prognostic and predictive significance in breast cancer and have important implications for tumor growth and metastatic patterns [1].

The 5-year local recurrence rate after breast conserving therapy varied by breast cancer subtypes [2].

Local and distant recurrence leads to poor survival outcome and the site of the distant recurrence is also important to predict the clinical outcome [3].

It has been reported that there is a significant difference in survival among the molecular subtypes of breast cancer [4].

However, data are limited regarding differences in distant recurrence sites between the breast cancer subtypes [5].

ER–/PR+ tumors have been associated with younger age, higher grade and HER2/neu overexpression, A retrospective study evaluated the clinical outcomes of ER–/PR+ breast cancer and revealed that they have a higher risk of relapse than ER+ tumors but lower than ER-/PR-, whereas overall survival more closely resembles ER+ disease [6].

This study aimed to assess the association of ER -ve / PR +ve breast cancer patients with clinicopathological characteristics, disease free survival and overall survival in comparison to ER +ve and to ER -ve and PR -ve tumors.

2. Patients and Methods

This retrospective study was conducted at the department of Clinical Oncology, Assiut University Hospital on records of 100 patients diagnosed with breast cancer between January 2008 and December 2012 . The study was reviewed and approved by the Ethics Committee of Faculty of Medicine, Assiut University before data collection.

Female patients with biopsy proven invasive ductal or lobular breast carcinoma -Stage I, II and III based on TNM staging system of the seventh edition American Joint Committee on Cancer (AJCC 2002 &AJCC 2010) staging for primary tumors of breast cancer [7,8], and patients treated by surgery followed by any adjuvant treatment (include radiotherapy, chemotherapy or endocrine therapy) were enrolled in the study.

Male patients were excluded from the study. Also patients were excluded if they had metastatic disease at presentation, no definitive surgery, incomplete medical records or follow-up status, unavailability of hormonal receptor status, carcinoma in situ or other rare tumors of the breast as phylloides tumors.

The following data were reviewed: Age of the patients - Menopausal status (premenopausal or postmenopausal) - Tumor size (<2 cm, 2-5 cm or >5 cm) - Lymph node involvement (positive or negative) - Stage of the disease - Histologic grade according to Elston and Ellis' criterion 1991- Hormonal receptor status.

Tumors from all patients were assessed for ER and PR status by immunohistochemistry. Tumors with ≥1% nuclear-stained cells were considered ER and/or PR positive according to the American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) guidelines [9].

In this study, we classified breast cancer patients into 3 hormonal receptors subtypes as follow: ER-/PR+ , ER+/PR±, and ER-/PR-

- **HER2 status:** HER2 positive cases were defined as immunohistichemistry score of 3+ according to the ASCO/CAP guidelines [10].
- **Primary surgery:** Breast conservative surgery (BCS) or mastectomy was done to all the patients.
- **Adjuvant radiotherapy:** Radiotherapy was indicated for the following: >3 lymph node positive, selective for patients with 1-3 lymph nodes metastasis, stage III and after BCS.
- **Adjuvant chemotherapy:** Chemotherapy was recommended for patients with lymph node positive and high risk lymph node negative except elderly women with ER or PR positive stage I breast cancer.
- **Adjuvant endocrine therapy:** All patients with ER or PR positive hormonal receptors in this study received endocrine therapy either by estrogen receptor modifier (tamoxifen 20 mg orally daily) or aromatase inhibitors (anastrazole 1 mg or letrozole 2.5 mg orally daily). Adjuvant estrogen receptor modifier was indicated in premenopausal women for 5 years while aromatase inhibitors were recommended for postmenopausal women for 3 years after 2 years of tamoxifen.
- **Assessment of recurrence:** Recurrence consisting of local (confined to ipsilateral breast or chest wall including mastectomy scars) or contralateral breast, regional nodes (including ipsilateral axillary, supraclavicular and internal mammary lymph nodes) or distant metastasis (including bone, lung, liver, brain or other organs). These recurrences foci were detected and proven through radiological studies or biopsy.
- **Estimation of disease-free survival and overall survival:** Disease-free survival was measured from the date of surgery to the date of the first documented local or distant recurrence. Overall survival was defined as the time from operation to death or last follow-up.
- **Comparison between the three hormonal receptor subtypes:** Analysis of the clinicopathological features, treatment, recurrence, survival rate and prognostic factors among the breast cancer three hormonal receptor subtypes.
- **Statistical analysis:** Data were revised and data entry was done. Clinicopathological characteristics were compared between the three hormonal receptor subtypes by Chi-square test. Disease-free survival and overall survival were calculated and compared using Kaplan-Meier method. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed by using SPSS version 22 (SPSS, Inc., Chicago. IL).

3. Results

In this retrospective study we analyzed the hospital records of 100 patients who were diagnosed with invasive breast cancer according to hormonal receptor status between January 2008 and December 2012 at Clinical Oncology Department, Assiut University Hospital.

Patient's and Disease Characteristics:

As shown in **Table (1)** the clinical characteristics of eligible patients. 8% (8 cases) were ER-PR+ as compared to 69.0% ER+PR± (69 cases), and 23% were ER-PR- (23 cases). The median age was as follow: ER-PR+ 44 years, ER+PR± 52 years, and 45 years for ER-PR-. The difference in median age between breast cancer hormonal receptor subtypes at diagnosis was statistically significant (*P*= 0.044).

Most of the cases were premenopausal patients (62.5%) in both ER-PR+ and ER-PR- **(Figure 1)**. On the other hand, most of the cases in ER+PR± group were postmenopausal (62.3%) and the difference was statistically significant (*P*= 0.005).

All cases of ER-PR+, 88.4% of ER+PR± and 87.0% of ER-PR- had tumor size from 2-5 cm **(Figure 2)**. The difference was statistically insignificant. Regarding nodal status, all patients with ER-PR+ had lymph nodes involvement while 68.1% and 78.3% of ER+PR± and ER-PR- patients respectively had positive nodal involvement **(Figure 3)**. The difference was statistically insignificant. The highest percentage of stage I& II tumors was observed in ER+PR± patients (71.0%) whereas, patients with ER-PR+ showed the highest presentation with stage III (37.5%) when compared with the other 2 subtypes but the difference was statistically insignificant. Categorization of the patients by the histological grading revealed that grade III tumors were more frequent in ER-PR+ (12.5%) and the difference also was insignificant statistically. As regard Her-2/neu status, 97.1% of the ER+PR±, 75% of the ER-PR+ and 87% of the ER-PR- patients were negative which was significantly higher than Her-2/neu positive in the three hormonal receptors subtypes (*P*= 0.02).

Table 1: Clinicopathologic Characteristics of breast cancer hormonal subtypes

Hormonal subtypes	ER+PR±	ER-PR+	ER-PR-	Significance
All cases, No. 100	No. 69 (%)	No. 8 (%)	No. 23 (%)	P-value
Median age/years	52	44	45	0.044*
Menopausal status				
Premenopausal	26 (37.7)	5 (62.5)	15 (62.5)	0.005*
postmenopausal	43 (62.3)	3 (37.5)	8 (34.8)	
Tumor size				
Less than 2cm	8 (11.6)	0 (0.00)	3 (13.0)	0.555
2-5 cm	61(88.4)	8 (100.0)	20 (87.0)	
Nodal status				
Negative	22 (31.9)	0 (0.00)	5 (21.7)	0.053
Positive	47 (68.1)	8 (100.0)	18 (78.3)	

AJCC stage group				
Stage I&II	49 (71.0)	5(62.5)	16 (69.6)	0.099
Stage III	20 (29.0)	3 (37.5)	7 (30.4)	
Histologic grade				
I/II	66 (95.7)	7 (87.5)	21 (91.3)	0.091
III	3 (4.3)	1 (12.5)	2 (8.7)	
Her-2/neu				
Negative	67(97.1)	6(75)	20(87.0)	0.029*
positive	2(2.9)	2(25)	3(13.0)	

ER= estrogen receptors, PR= progesterone receptors, AJCC= American Joint Committee on Cancer, HER-2/neu= Human Epidermal Growth Factor-2, *= significant values.

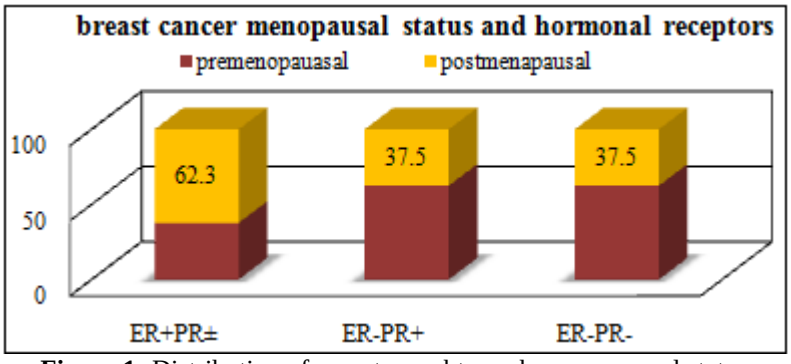

Figure 1: Distribution of receptors subtypes by menopausal status

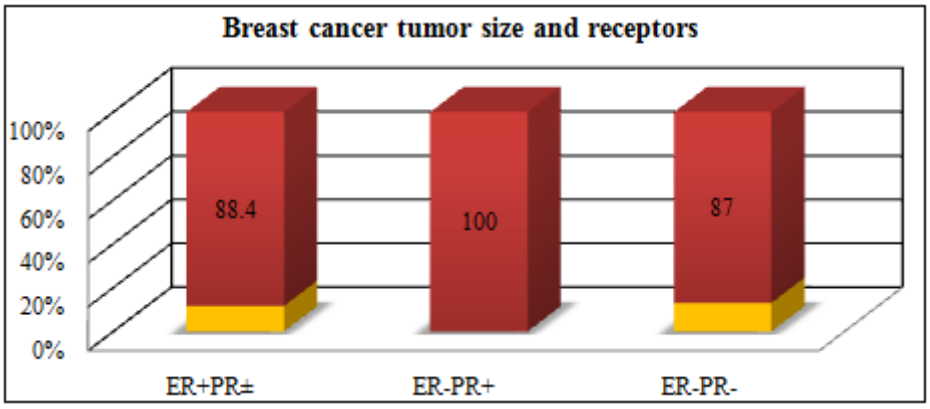

Figure 2: Distribution of receptors subtypes by tumor size

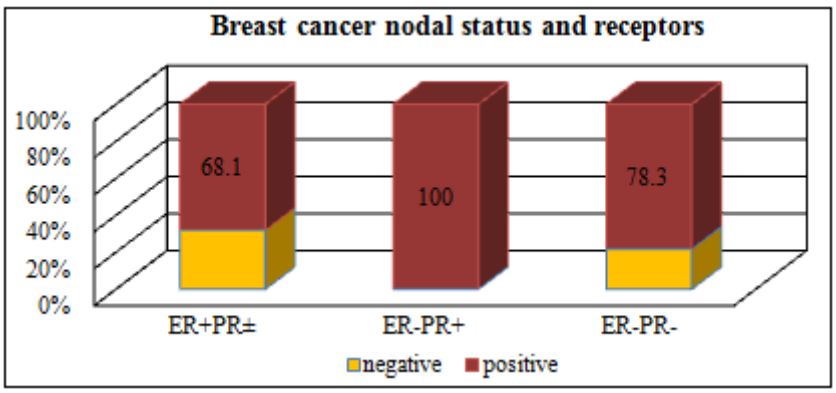

Figure 3: Distribution of receptors subtypes by nodal status

Table (2) shows the different therapeutic strategies of breast cancer patients; mastectomy was the dominant surgical approach in the three breast cancer hormonal subtypes. As regards adjuvant chemotherapy, anthracycline-based regimen was the most commonly used regimen. Adjuvant radiotherapy was prescribed to 65-75% of the patients. Surgery, adjuvant chemotherapy and radiotherapy treatment were not statistically different among the cohort of different breast cancer hormonal receptor subtypes. However, significant difference was noted in adjuvant hormonal systemic therapy. The proportion of adjuvant hormonal treatment was obviously lower (13.0% vs. 87%) in ER-PR- than in the other 2 hormonal receptor subtypes (P>0.001).

Table 2: Treatment of different breast cancer hormonal subtypes

Hormonal receptors	ER+PR±	ER-PR+	ER-PR-	Significance
All cases No. 100	No. 69	No.8	No.23	P-value
Primary surgery				
-BCS	8 (11.6)	1(12.5)	4 (17.4)	
-Mastectomy	61 (88.4)	7 (87.5)	19 (82.6)	0.291
Adjuvant chemotherapy				
-No	4 (5.8)	0 (0.00)	1 (4.3)	
-Anthracyclin-based	62 (89.9)	6 (75.0)	22 (95.7)	0.077
-Taxane based	1 (1.4)	1 (12.5)	0 (0.00)	
-CMF	2 (2.9)	1 (12.5)	0 (0.00)	
Adjuvant radiotherapy				
-Yes	48(69.6)	6(75)	15(65.2)	
-No	21(30.4)	2(25)	8(34.8)	0.282
Adjuvant endocrine treatment				
-Yes	60 (87.0)	7 (87.5)	3 (13.0)	0.001*
-Tamoxifen	44 (73.3%)	5(71.4%)	3 (100.0)	
-AI	16 (26.7%)	2 (28.6%)	0 (0.00)	
-No	9 (13%)	1 (12.5%)	20 (87.0%)	

ER=estrogen receptors, PR= progesterone receptors, BCS= breast conservative surgery, AI= aromatase inhibitors, *= significant value, CMF= cyclophosphamide, methotrexate and 5-fluorouracil regimen

By analysis of the Frequency of recurrence and death among different breast cancer hormonal receptor subtypes we found that local recurrence was higher in ER+PR± (7.2%), distant metastasis was observed in 50% of cases of the same group while the number of deaths was the same (87%) for the 3 subtypes with no statistical significant difference. As shown in **Table (3).**

Table 3: Frequency of recurrence and death among different breast cancer hormonal receptor subtypes

Variables	Hormonal receptors subgroups						P value
	ER + PR +/-		ER – PR +		ER – PR -		
	No.69	%	No.8	%	No.23	%	
Recurrence†							
-Yes	5	7.2	0	0.00	1	4.3	0.237
-No	64	92.8	8	100.00	22	95.7	
Distant metastasis							
-Yes	34	49.3	4	50.0	8	34.8	0.050
-No	35	50.7	4	50.0	15	65.2	
Death							
-No	60	87.0	7	87.5	20	87.0	0.130
-Yes	9	13.0	1	12.5	3	13.0	

ER=estrogen receptors, PR= progesterone receptors, Recurrence †= local, regional or contralateral breast

To evaluate the effect of prognostic factors on the overall survival various clinicopathologic variables were analyzed in the three subtypes of breast cancer as shown in **Table (4).** Postmenopausal status and negative lymph nodes were significant prognostic factors for longer survival **(Figures 4 and 5).**

Table 4: Analysis of overall survival in different breast cancer hormonal receptors subtypes

	ER + PR +/-		ER – PR +		ER – PR -		Total		P value
	No.69 Mean	±SD	No.8 Mean	±SD	No.23 Mean	±SD	No.100 Mean± SD		
Menopausal status									
-Premenopausal	4.3	±1.4	4.0	±.00	3.9	±1.7	4.6	±1.6	0.005
-Postmenopausal	5.7	±1.5	5.3	±1.6	4.0	±1.4	5.6	±1.7	
Tumor size									
-<2 cm	4.4	±1.5	0.00		3.9	±1.7	5.2	±1.5	0.294
-2-5 cm	4.3	±.74	5.00	±1.5	4.0	±1.4	4.6	±1.8	
Nodal status									
-Negative	4.5	±1.5	0.00		3.9	±1.1	5.8	±1.9	0.015
-Positive	4.3	±1.4	5.00	±1.5	3.6	±1.8	4.9	±1.6	
Stage									
-Stage I& II-	4.4	±1.4	5.6	±1.5	4.0	±1.2	5.3	±1.7	0.178
-Stage III-	4.4	±1.5	4.6	±1.5	3.8	±1.9	4.8	±1.7	
Histologic grade									
-Grade I&II-	4.5	±1.4	5.3	±1.3	4.5	±1.7	5.1	±1.8	0.478
-Grade III-	3.0	±1.0	3.0	±0.0	3.8	±0.7	4.6	±1.4	

ER=estrogen receptors, PR= progesterone receptors, ±SD= standard deviation

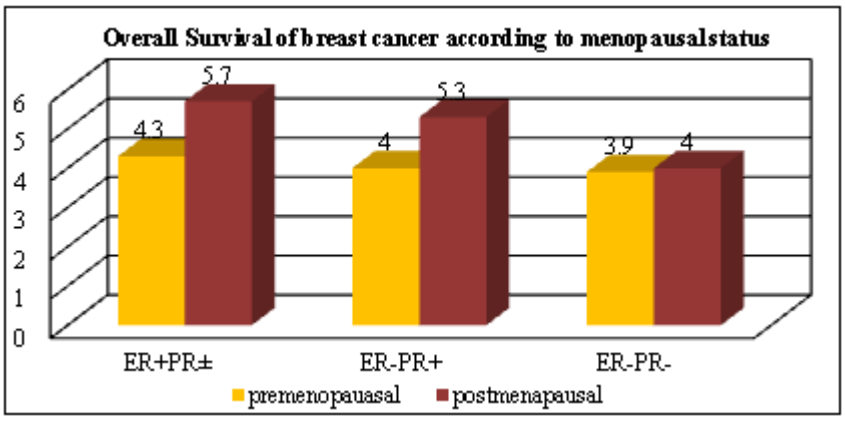

Figure 4: Overall survival rate shows significant differences among premenopaual & postmenopausal 3 hormonal receptor subtypes (P= 0.005)

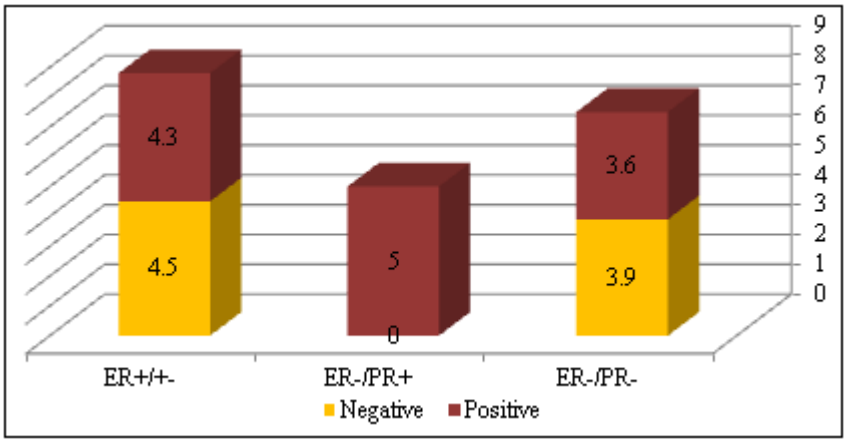

Figure 5: Overall survival rate shows significant differences among lymph node negative& positive of breast cancer hormonal receptor subtypes (P= 0.015)

By analyzing the disease free survival (DFS) and overall survival (OS) among different breast cancer hormonal receptor subtypes, we found that the lowest mean DFS and OS were observed in ER-PR- subtype but the difference was not statistically significant as shown in **Table (5)** and **figure (6)**.

Table 5: Disease free survival and overall survival in different breast cancer hormonal subtypes

	ER +/PR ± No. (69)	ER -/ PR + No. (8)	ER -/ PR - No. (23)	P Value
Disease free survival				
-5-year, N (%)	14(20.3%)	3 (37.5%)	5 (21.7%)	0.196
-Mean ±SD	3.04±2.1	3.25±2.7	2.7±2.03	
Overall Survival				
-5-year, N (%)	23 (33%)	4 (50%)	8 (34.8%)	0.094
-Mean ± SD	4.42±1.5	5±1.5	3.9±1.7	

ER= estrogen receptor, PR= progesterone receptor, ± SD= standard deviation

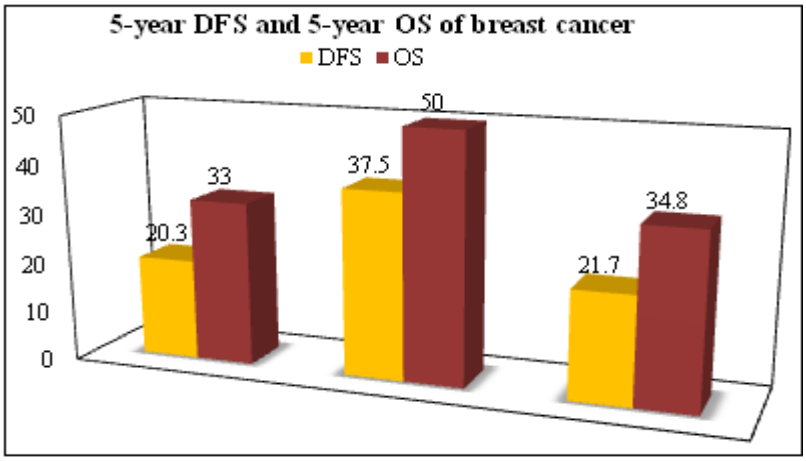

Figure 6: Disease-free survival (DFS) & 5-year overall survival (OS) according to 3 breast cancer hormonal subtypes (P=0.19, P=09)

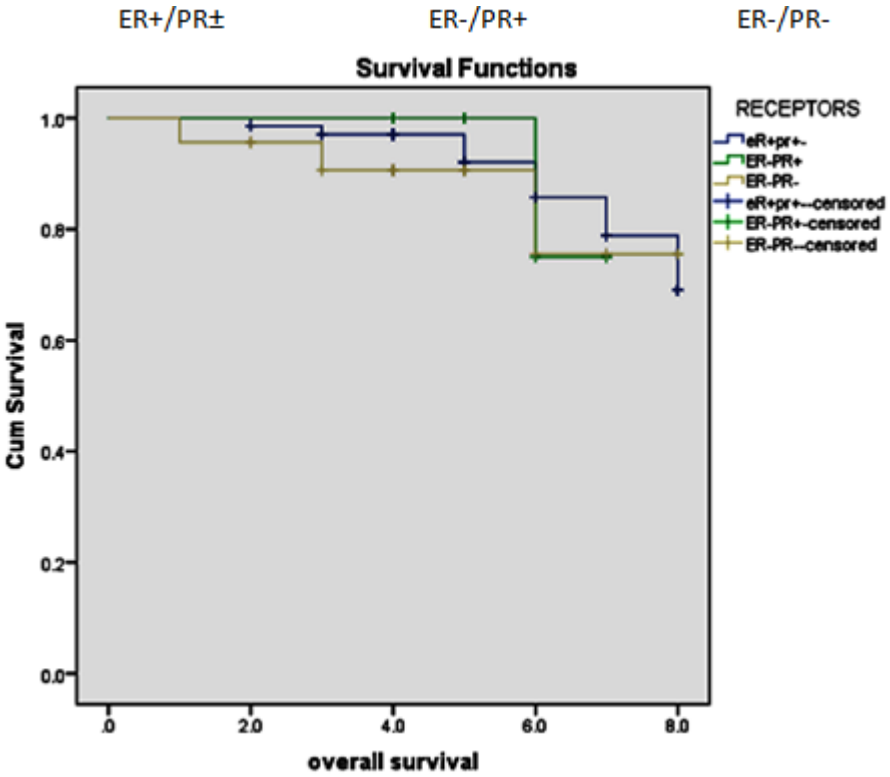

Figure 6: Disease-free survival (DFS) & 5-year overall survival (OS) according to 3 breast cancer hormonal subtypes (P=0.19, P=09)

4. Discussion

Breast cancer is the second most common cancer in women worldwide ***(International Agency for researches in Cancer 2014***). It comprises about 25% of invasive cancers in women ***(World Health Organization 2015).***

The age standardized rate (per 100.000) of breast cancer was as follow: In Africa 36.2, America 67.6, Asia 29.1 and Europe 71.1were estimated [11].

In Egypt the incidence of breast cancer among women was estimated to be 33.5% and 21.6% of cancer mortality ***(GLOBOCAN 2012)***.

Breast cancer is demonstrating heterogeneity at the molecular, histopathologic and clinical levels. Gene expression studies have identified molecularly distinct subtypes with prognostic significance [12].

Gene expression profiling can be used to separate breast cancer into molecular subtypes which has a prognostic significance [13]. Assays based on gene expression profiling including Oncotype DX and MammaPrint may provide useful prognostic information [14].

Immunohistochemical (IHC) has been validated as a method for molecular profiling [15] and can provide much of the prognostic information obtained by gene expression profiling [16].

Several subtypes of breast cancer have been established according to the genetic and molecular analysis based on estrogen receptor (ER), progesterone receptor (PR) and Her-2 status. The subtypes are: Luminal A (ER+ and/or PR+, Her-2 negative), Luminal B (ER+ and/or PR+, Her-2±), Her-2 enriched (Her-2+/ER& PR-) and basal-like (ER-, PR-, Her-2-) this last subtype also commonly referred to as triple negative breast cancer. These molecular subtypes had prognostic implications across multiple treatment decisions[17].

Among these markers, ER and Her-2 have settled their positions as prognostic factors and there is a lack of knowledge about the role of PR in breast cancer [18].

Single PR positivity was believed to be a rare phenomenon but recent researches support that it is accounting for 3.4% to 7% of total cases [19].

Progesterone receptor status was found to be a strong prognostic factor for survival and ER-/PR+ tumors might have biologic characteristics in between ER+/PR+ and ER+/PR- [20].

In our study one hundred female breast cancer patients with different hormonal group subtypes were studied. We have investigated in detail the clinical features and outcomes of the three different molecular subtypes (ER+/PR±, ER-/PR+, & ER-/PR-) and their associations with other prognostic variables.

Our study revealed that breast cancer patients with ER-/PR+ tumor constituted 8% of cases when compared with ER+/PR± and ER-/PR- tumors which constituted 69% and 23% respectively. These figures are consistent with the previously published studies.

Cserni et al 2011 reported that a range of 0.3-7.1% of cases of breast cancer had ER-PR+ status by IHC from 9 Hungarian departments [21].

Another study done by Yu et al 2008 showed that 11.2% of consecutive operable patients with breast cancer were ER-/PR+ tumors and 34.5% of cases were ER+/PR+ tumors [22].

Kurbel et al 2013 reported that the existence of breast cancer with phenotype ER+/PR± makes 78% and ER-/PR+ 3.06% and ER-/PR- were 18.48%. So, the previous studies including ours support the information regarding rarity of ER-/PR+ hormonal subtype [23].

The subtype ER-/PR+ tumor in the present study was seen frequently in young age premenopausal women with large size and lymph node metastasis, higher stage and histologic grade when compared with the other two hormonal subtypes. These results were in agreement with the results of the study done by Yu et al 2008 who reported that patients with ER-/PR+ tumors were younger than patients with ER+/PR+ tumors and were mainly premenopausal, had more involved lymph nodes and later stage at diagnosis [22].

The same figures were also reported by Rakha et al 2007. They found that ER+/PR- tumors more frequently found in elderly, postmenopausal women and the majority were grade II, no difference between the two groups in lymph node stage [24].

More recently, Mattes et al 2015 also examined a large series of 7.274 breast cancer cases focusing on the subtype that can predict advanced nodal stage. They found that triple-negative cancer had a significantly lower risk of nodal positivity than the hormonal receptor (HR) positive/Her-2 negative subtype but there was no difference in lymph node positivity between PR+ and PR- tumors amongst ER+/Her-2- or ER+/Her-2+ tumors [25].

The majority of the patients in our study were Her-2 negative while the study done by Azizun-Nisa et al 2008 to assess ER, PR and Her-2/neu reactivity pattern of mammary cancers revealed that ER and PR expression was significantly lower in Her-2/neu positive as compared with Her-2/neu negative tumors [26].

The primary surgical treatment in our study did not differ between the three subtypes, these results were not consistent with the results of the study done by Cancello et al 2013 who reported that the ER+/PR-/Her-2± subgroup was associated with a significant reduced breast conservative surgery when compared with the ER+/PR+/Her-2± subgroup [27].

In the present study, the adjuvant taxane-based (12.5% vs. 1.4% and 0.0%) regimen was commonly used in ER-/PR+ group when compared with ER± and ER-/PR-subtypes. This can be explained by the presence of high risk factors in ER-/PR+ subtype as larger tumor size, more involved lymph nodes and higher percentage of grade III histology.

As regard adjuvant endocrine treatment, which was significantly lowest in the ER-/PR- subtype when compared with the positive hormonal receptor subtypes in the current study which can be explained by the fact that HR testing is a predictor marker for endocrine therapy in the clinical management of breast cancer.

Yu et al 2008 found that ER-/PR+ group got more benefit from CMF regimen than from CA(E)F regimen and in addition significant increase in survival rate was observed between the tamoxifen treated ER+/PR+ group than ER-/PR+ group either in disease=free survival (DFS) and overall survival (OS) [22].

Analysis of the frequency of recurrence in our study revealed that local recurrence, distant metastasis and number of deaths did not differ statistically and hence no difference in DFS and OS but the ER-/PR- subtype showed the worst DFS and OS. These results were comparable to the results of the study done by Akinyemiju et al 2015 who reported that Her-2+/HR- cases had significantly higher hazards of cancer related deaths compared with Her-2+/HR+ cases [28].

Another study done by Latiano et al 2010 showed that PR- cases were associated with worst DFS and OS compared with PR+ cases [29].

Chan et al 2014 examined the association of ER-/PR+ with time to relapse and OS in comparison to ER+ and ER-/PR- tumors. They found that ER-/PR+ tumors have higher risk of relapse than ER+ tumors but lower than ER-/PR- tumors. The timing of relapse of ER-/PR+ more closely resemble ER-/PR- disease whereas OS resemble ER+ disease [30].

A recent study done by Fan et al 2015 showed the reverse of the results of the previous study. They found no difference between ER-/PR+/Her-2- and triple negative breast cancer patients in relapse-free survival and OS [31].

Analysis of the prognostic factors in our study for patients with different breast cancer subtypes showed that adjuvant chemotherapy, radiotherapy and endocrine treatment were identified as prognostic factors for a better OS.

In other analysis, patients with ER-/PR+/Her-2- tumors receiving adjuvant endocrine therapy had a significant more favorable prognosis of DFS but axillary lymph node metastasis was an independent adverse prognostic factor for both DFS and OS as reported by Fan et al 2015 [31].

Comparable results were also reported by Chan et al 2014 who found that nodal status and HR- group was associated with worse OS in multivariate analysis [30].

Another study done by Xue et al 2012 showed that lower age, larger tumor size, lymph node positive status, American Joint Committee on Cancer Staging stage III, negative hormonal receptor status, Her-2/neu positive, histologic grade III, lympho-vascular invasion and high Ki-67 were adverse prognostic factors for DFS and OS when analyzed by univariate and multivariate analysis among different breast cancer subtypes [32].

5. Conclusion

We have identified biologic and outcome differences between ER–/PR+ and other hormonal subtypes confirming that the breast cancer subtypes according to the ER and PR are biologically and clinically different groups so we suggest that consideration be given to exploring the behavioral characteristics of these tumors with respect to treatment response in more detail.

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